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Gene Section
Mini Review

FLT3 (FMS-like tyrosine kinase 3)

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Identity

Other names: CD135; FLK2 (Fetal liver kinase 2); STK1 (Stem cell kinase 1)

HGNC (Hugo): FLT3

Location: 13q12.2

DNA/RNA

Description

The FLT3 gene contains 24 exons and spans 96,982 bases (start: 27,475,753 bp to end 27,572,735 from 13pter) oriented at the minus strand.

Transcription

3.7 kb; 2979 bp open reading frame.

Protein

Description

Size: 993 amino acids; 112804 Da; FLT3 is a class III receptor tyrosine kinase (RTK) structurally related to the receptors for platelet derived growth factor (PDGF), colony stimulating factor 1 (CSF1), and KIT ligand (KL).; these RTK contain five immunoglobulin-like domains in the extracellular region and an intracelular tyrosine kinase domain splitted in two by a specific hydrophilic insertion (kinase insert); immunoprecipitation of the human FLT3 protein results in the appearance of a minor band of Mr 130 000 and a major band of Mr 155 000/160 000; the high-molecular-weight band corresponds to the mature, N-glycosylated form, and the low-molecular-weight band to the immature, high mannose-containing form; N-linked glycosylations account for 50 000 daltons.

Expression

FLT3 expression was described on bone marrow CD34-positive cells, corresponding to multipotential, myeloid and B-lymphoid progenitor cells, and on monocytic cells; FLT3 expression is restricted to cells of the fetal liver expressing high levels of CD34; in addition, the FLT3 protein is expressed on blast cells from most ANLL and B-ALL.

Localisation

Subcellular location: Type I membrane protein. 3D structure: PDB id 1RJB (3D).

Function

FLT3 receptor function can be defined by the activity of its ligand (FL); FL is an early acting factor and supports the survival, proliferation and differentiation of primitive hemopoietic progenitor cells. Ligand binding to FLT3 promotes receptor dimerization and subsequent signalling through posphorylation of multiple cytoplasmatic proteins, including SHC, SHP-2, SHIP, Cbl, Cbl-b, Gab1 and Gab2, as well as the activation of several downstream signalling pathways, such as the Ras/Raf/MAPK and PI3 kinase cascades.
Function: Receptor for the FL cytokine. Has a tyrosine-protein kinase activity. Catalytic activity: ATP + a protein tyrosine = ADP + protein tyrosine phosphate.
Similarity: Belongs to the Tyr protein kinase family. CSF-1/PDGF receptor subfamily. Contains 1 immunoglobulin-like C2-type domain.

Homology

Other tyrosine kinases: KIT, PDGFRA, PDGFRB, VEGFR.

Mutations

Somatic

Mutations in the FLT3 gene are the most frequent genetic aberration that have been described in acute myeloid leukemia. With 20-25% length mutations in the juxtamembrane domain are the most frequent, followed by 7-8% mutations in the second tyrosine kinase kinase domain, mostly point mutations in codon 835 or deletions of codon 836. Also point mutations in the juxta membrane domain have been described and the number of new mutations all over the total gene is still growing.

Implicated in

FLT3-length mutation (FLT3-LM)

Disease

Internal tandem duplications and/or insertions and, rarely, deletions in the FLT3-gene are implicated in 20-25% of all acute myeloid leukemias (AML). It was also described to be involved in 5-10 % myelodysplastic syndromes (MDS) refractory anaemia with excess of blasts (RAEB 1 and RAEB 2) and rare cases with acute lymphoblastic leukemia (ALL) The duplicated sequence belongs to exon 11 but sometimes involves intron 11 and exon 12. The most frequently used nomenclature is FLT3-ITD (internal tandem duplication). Because of the very heterogenous molecular structure the term FLT3-LM (length mutation) seems to be more adequate.

Prognosis

An unfavourable impact on prognosis especially a high relapse rate of the FLT3-LM has been shown by many study groups. Patients with loss of the wildtype allele have an even worse prognosis than the mutated with retention of the wildtype allele. Perspective: It is of special interest that this mutation allows to perform PCR-based minimal residual disease detection in a high number of these high risk AML patients.

Cytogenetics

FLT3-LM are highly correlated with a) normal karyotype, b) t(15;17)(q25;q21) c) Perspective: It is of special interest that this mutation allows to perform PCR-based minimal residual disease detection in a high number of these high risk AML patients.

Oncogenesis

This mutation leads to constitutive ligand independent autophosphorylation of the receptor. The FLT3-LM vary in size and position in a nearly patient specific manner. Overall the aberrant structure of the juxtamembrane domain disrupts a
negative regulatory domain, which leads to the constitutive receptor activation. Several Groups have reported qualitative differences in the intracellular signals provided by wild type and mutated receptors.Mutated receptor weakly works through MAP kinase and Akt but instead through strong and constitutively activated STAT5.

FLT3 Tyrosine Kinase Domain Mutation (FLT3-TKD)

Disease

In the second tyrosine kinase domain point mutations and small deletions mostly of codons 835 and 836, respectively, can be found in 7-8% of all AML.

Prognosis

No independent impact on prognosis shown yet.

Cytogenetics

In contrast to the FLT3-LM they do not seem to be specifically correlated to a certain AML type.

Oncogenesis

These mutations also lead to constitutive autoactivation of the receptor. It has been suggested that TKD mutation may both trigger the activation loop and stabilize it in the active state.

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